PROFESSIONAL INFORMATION

OSELTREX

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

OSELTREX 75 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains oseltamivir phosphate equivalent to 75 mg oseltamivir.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

The tablets are white, round, biconvex.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment: OSELTREX is indicated for the treatment of influenza in adults and children weighing 40 kg or more (see section 4.2).

Prophylaxis: OSELTREX is indicated for the prophylaxis of influenza in adults and children weighing 40 kg or more (see section 4.2).

4.2 Posology and method of administration

Posology

Treatment of influenza

Treatment should be initiated within the first or second day of onset of symptoms of influenza.

Adults and adolescents 13 years and older: The recommended oral dose is one OSELTREX tablet twice daily for 5 days.

Children weighing 40 kg or more: Children weighing > 40 kg, who are able to swallow tablets, may also receive treatment with OSELTREX. The recommended oral dose is one OSELTREX tablet twice daily for 5 days.

Prophylaxis of influenza

Adults and adolescents: The recommended oral dose for the prophylaxis of influenza following close contact with an infected individual is one OSELTREX tablet once daily for at least 10 days. Therapy should be initiated within two days of exposure.

The recommended dose for prophylaxis during a community outbreak of influenza is one OSELTREX tablet once daily. Safety and efficacy have been demonstrated for up to six weeks. The duration of protection lasts as long as dosing is continued.

Children weighing 40 kg or more: Children weighing > 40 kg, who are able to swallow tablets, may also receive treatment with OSELTREX. The recommended oral dose is one OSELTREX tablet once daily for 10 days.

Special populations

Renal impairment

Treatment of influenza:

No dose adjustment is necessary for patients with creatinine clearance above 60 mL/min. In patients with a creatinine clearance of > 30 – 60 mL/min, it is recommended that the treatment dose be reduced to 30 mg oseltamivir twice daily for 5 days, and in patients with a creatinine clearance of 10 – 30 mL/min, it is recommended that the dose be reduced to 30 mg oseltamivir

once daily for 5 days. Therefore, OSELTREX should not be used in patients with renal impairment with a creatinine clearance below 60 mL/min and an alternative oseltamivir-containing medicine of the appropriate strength should be used.

OSELTREX should not be used in patients undergoing routine haemodialysis and peritoneal dialysis: in patients undergoing routine haemodialysis an initial dose of 30 mg oseltamivir can be administered prior to the start of dialysis if influenza symptoms develop during the 48 hours between dialysis sessions and, to maintain plasma concentrations at a therapeutic level, a dose of 30 mg should be administered after every haemodialysis session; for peritoneal dialysis an initial dose of 30 mg oseltamivir administered prior to the start of dialysis followed by further 30 mg doses administered every 5 days is recommended for treatment. Therefore, an alternative oseltamivir-containing medicine of the appropriate strength should be used in patients undergoing routine haemodialysis and peritoneal dialysis.

The pharmacokinetics of oseltamivir, as contained in OSELTREX, have not been studied in patients with “end-stage renal disease” (i.e. creatinine clearance < 10 mL/min) not undergoing dialysis. Hence, dosing recommendation cannot be provided for this group (see sections 4.4 and 5.2).

Prophylaxis of influenza:

No dose adjustment is necessary for patients with creatinine clearance above 60 mL/min. In patients with a creatinine clearance between > 30 – 60 mL/min, it is recommended that the treatment dose be reduced to 30 mg oseltamivir once daily, and in patients with a creatinine clearance of 10 – 30 mL/min, it is recommended that the dose be reduced to 30 mg oseltamivir every other day. Therefore, OSELTREX should not be used in patients with renal impairment with a creatinine clearance below 60 mL/min and an alternative oseltamivir-containing medicine of the appropriate strength should be used.

OSELTREX should not be used in patients undergoing routine haemodialysis and peritoneal dialysis: in patients undergoing routine haemodialysis an initial dose of 30 mg oseltamivir can be administered prior to the start of dialysis and to maintain plasma concentrations at a therapeutic

level, a dose of 30 mg should be administered after every alternate haemodialysis session; for peritoneal dialysis an initial dose of 30 mg oseltamivir administered prior to the start of dialysis followed by further 30 mg doses administered every 7 days is recommended for prophylaxis. Therefore, an alternative oseltamivir-containing medicine of the appropriate strength should be used in patients undergoing routine haemodialysis and peritoneal dialysis.

The pharmacokinetics of oseltamivir, as contained in OSELTREX, have not been studied in patients with “end-stage renal disease” (i.e., creatinine clearance < 10 mL/min) not undergoing dialysis. Hence, dosing recommendation cannot be provided for this group (see sections 4.4).

Hepatic impairment

No dose adjustment is required for patients with mild or moderate hepatic dysfunction in the treatment or prophylaxis of influenza (see section 5.2, Special Populations). The safety and pharmacokinetics in patients with severe hepatic impairment have not been studied.

Elderly

No dose adjustment is required for elderly patients in the treatment or prophylaxis of influenza (see section 5.2, Special Populations).

Immunocompromised patients

Seasonal prophylaxis in immuno-compromised adults and children weighing 40 kg or more, who are able to swallow tablets, is recommended for 12 weeks. No dose adjustment is necessary.

Children

The safety and efficacy of oseltamivir, as contained in OSELTREX, in children under 1 year has not been established. Furthermore, OSELTREX is only indicated in children weighing 40 mg or more, who are able to swallow tablets.

Method of administration

Oral use.

The tablets should be swallowed whole with water. OSELTREX may be taken with or without food (see section 5.2, Absorption). However, in some patients, taking OSELTREX with food may enhance tolerability.

4.3 Contraindications

Hypersensitivity to the active substance, oseltamivir, or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Neuropsychiatric events

Neuropsychiatric events such as convulsions, abnormal and inappropriate behaviour, disturbances in consciousness, hallucinations and delirium have been reported during administration of oseltamivir, as in OSELTREX, in patients with influenza, especially in children and adolescents. In some cases, the delirium resulted in accidental self-injury and death. These events occurred mostly within the first few days of taking oseltamivir. Patients, and especially paediatric and adolescent patients, should be closely monitored for behavioural changes, and signs of abnormal behaviour.

OSELTREX effectiveness and suitability for use

OSELTREX is effective only against illness caused by influenza viruses. There is no evidence for efficacy of oseltamivir in any illness caused by viruses other than influenza virus types A and B. OSELTREX is not a substitute for influenza vaccination.

Resistance of influenza viruses to oseltamivir have been reported. The prevalence of virus resistance and virus strains on subtypes differs between countries and seasons. Updated local surveillance data from the National Institute for Communicable Diseases (NICD) should be consulted for information on seasonal prevalence of medicine resistant viruses.

OSELTREX is not a substitute for influenza vaccination. The use of OSELTREX must not affect the evaluation of individuals for annual influenza vaccination. The protection against influenza lasts only as long as OSELTREX is administered. OSELTREX should be used for the treatment and prevention of influenza only when reliable epidemiological data indicate that influenza virus is circulating in the community.

Renal impairment

Dose adjustment is recommended for patients with creatine clearance of 10 – 60 mL/min for both treatment and prevention. No dosing recommendation is available for patients with end-stage renal disease and for patients with creatinine clearance of ≤ 10 mL/min (see sections 4.2 and 5.2).

Paediatric population

The safety and efficacy of oseltamivir, as contained in OSELTREX, in children under 1 year has not been established. Furthermore, OSELTREX is only indicated in children weighing 40 mg or more, who are able to swallow tablets.

4.5 Interaction with other medicines and other forms of interaction

Pharmacokinetic properties of oseltamivir, as in OSELTREX, such as low protein binding and metabolism independent of the CYP450 and glucuronidase systems (see section 5.2), suggest that clinically significant medicine interactions via these mechanisms are unlikely.

There is no mechanistic basis for an interaction with oral contraceptives.

Renal elimination

Clinically important medicine interactions involving competition for renal tubular secretion are unlikely, due to the known safety margin for most of these substances, the elimination characteristics of the active metabolite (glomerular filtration and anionic tubular secretion) and the excretion capacity of these pathways. However, care should be taken when prescribing

OSELTREX in subjects when taking co-excreted medicines with a narrow therapeutic margin (e.g. chlorpropamide, methotrexate, phenylbutazone).

Probenecid

Co-administration of probenecid results in approximate 2-fold increase in exposure to the active metabolite due to a decrease in active tubular secretion in the kidney. However, due to the wide safety margin of the active metabolite, no dose adjustments are required when co-administering with probenecid.

Amoxicillin

Co-administration with amoxicillin does not alter plasma levels of either compound, indicating that competition for the anionic secretion pathway is weak.

Paracetamol

Co-administration with paracetamol does not alter plasma levels of OSELTREX, its active metabolite, or paracetamol.

Additional information

No pharmacokinetic interactions between oseltamivir, as in OSELTREX, or its major metabolite have been observed when co-administering oseltamivir with paracetamol, acetylsalicylic acid, cimetidine, antacids (magnesium and aluminium hydroxides and calcium carbonates), amantadine or warfarin.

It is documented that no change in adverse event profile or frequency has been observed when oseltamivir was co-administered with commonly used medicines such as (bendrofluazide), antibiotics (penicillin, cephalosporin, azithromycin, erythromycin and doxycycline), H_2-receptor blockers (ranitidine, cimetidine), beta-blockers (propranolol), xanthines (theophylline),

sympathomimetics (pseudoephedrine), opioids (codeine), corticosteroids, inhaled bronchodilators, and analgesic medicines (aspirin, ibuprofen and paracetamol).

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established.

Pegnancy

The use of OSELTREX during pregnancy is not recommended. No controlled clinical trials have been conducted on the use of OSELTREX in pregnant women.

Breastfeeding

It is documented that low levels of oseltamivir and the active metabolite were detected in breastmilk. Safety in humans has not been demonstrated in children of breastfeeding women using OSELTREX. Mothers on treatment with OSELTREX should not breastfeed their infants.

Fertility

Based on preclinical data, there is no evidence that oseltamivir has an effect on female or male fertility.

4.7 Effects on ability to drive and use machines

OSELTREX may cause an altered level of consciousness, delirium, convulsion, and visual disturbances which may influence the ability of the patient to drive and use machines (see section 4.8). Therefore, patients should be advised not to drive or operate machinery if they experience these side-effects.

4.8 Undesirable effects

a. Summary of the safety profile

In adults and adolescents, the most commonly reported side effects were nausea, vomiting, pain and headache. The majority of these side effects were reported on a single occasion on either the first or second treatment day and resolved spontaneously within 1 to 2 days. In children, the most commonly reported adverse reaction was vomiting.

The following serious adverse reactions have been rarely reported since oseltamivir has been marketed: Anaphylactic and anaphylactoid reactions, hepatic disorders (fulminant hepatitis, hepatic function disorder and jaundice), angioneurotic oedema, Stevens-Johnson syndrome and toxic epidermal necrolysis, gastrointestinal bleeding and neuropsychiatric disorders.
(Regarding neuropsychiatric disorders, see section 4.4.)

b. Tabulated list of adverse reactions

System Organ Class	**Frequency**	**Adverse reactions**
Infections and infestations	Frequent	Bronchitis*, sinusitis* herpes simplex, nasopharyngitis, upper respiratory tract infections, influenza, otitis media+, pneumonia+
Blood and lymphatic system disorders	Less frequent	Thrombocytopenia, lymphadenopathy+
Immune system disorders	Less frequent	Hypersensitivity reactions, anaphylactic reactions, anaphylactoid reactions

System Organ Class	Frequency	Adverse reactions
Psychiatric disorders	Less frequent	Agitation, abnormal behaviour, anxiety, confusion, delusions, delirium, hallucination, nightmares, self-injury
Nervous system disorders	Frequent	Headache*, insomnia
	Less frequent	Altered level of consciousness, convulsion
Eye disorders	Frequent	Conjunctivitis (including red eyes, eye discharge and eye pain)[+]
	Less frequent	Visual disturbance
Ear and labyrinth disorders	Frequent	Earache[+]
	Less frequent	Tympanic membrane disorder[+]
Cardiac disorders	Less frequent	Cardiac dysrhythmia

System Organ Class	Frequency	Adverse reactions
Respiratory, thoracic and mediastinal disorders	Frequent	Cough*, nasal congestion*, sore throat, rhinorrhoea*, asthma (incl. aggravated)[+], epistaxis[+]
Gastrointestinal disorders	Frequent	Nausea*, vomiting*, abdominal pain (incl. upper abdominal pain)*, dyspepsia*, diarrhoea*
	Less frequent	Gastrointestinal bleedings, haemorrhagic colitis
Hepatobiliary disorders	Less frequent	Elevated liver enzymes, fulminant hepatitis, hepatic failure, hepatitis

System Organ Class	Frequency	Adverse reactions
Skin and subcutaneous tissue disorders	Frequent	Dermatitis (including allergic and atopic dermatitis)[+]
	Less frequent	Eczema, dermatitis, rash, urticaria, angioneurotic oedema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis
Musculoskeletal, connective tissue and bone disorders	Frequent	Back pain, arthralgia, myalgia
Reproductive system and breast disorders	Frequent	Dysmenorrhoea
General disorders and administrative site conditions	Frequent	Pain, dizziness (incl. vertigo), fatigue, pyrexia, influenza-like illness, limb pain

*ADR reported with use in all age groups, including the paediatric population (children aged 1 – 12 years).

[+]ADR reported with use of oseltamivir, as in OSELTREX, in the paediatric population (children aged 1 – 12 years) only.

c. Description of selected adverse reactions

Psychiatric disorders and nervous system disorders: Neuropsychiatric events such as convulsions, abnormal and inappropriate behaviour, including abnormal motor behaviour, disturbances in consciousness, hallucinations and delirium have been reported post-marketing. In some cases, the delirium resulted in accidental self-injury and death. More events were reported in males than in females. These neuropsychiatric events occurred mostly within the first few days of administration of oseltamivir. Patients, especially paediatric and adolescent patients should therefore be carefully monitored for abnormal behaviour for the first few days. Convulsions and psychiatric symptoms have also been reported in patients with influenza who were not taking oseltamivir.

Hepato-biliary disorders: Hepato-biliary system disorders, including hepatitis and elevated liver enzymes in patients with influenza-like illness. These cases include fatal fulminant hepatitis resulting in fatal outcomes and/or hepatic failure.

Gastrointestinal disorders: Gastrointestinal bleedings, in particular, haemorrhagic colitis was reported that subsided when the course of influenza abated or treatment with OSELTREX was interrupted.

d. Paediatric population

Children with pre-existing bronchial asthma: In general, the adverse reaction profile in children with pre-existing bronchial asthma was qualitatively similar to that of otherwise healthy children.

e. Other special populations

The elderly and patients with chronic cardiac and/or respiratory disease: In general, the safety profile of these patients were qualitatively similar to that in otherwise healthy adults and/or adolescents.

Immunocompromised patients

The safety profile of oseltamivir as in OSELTREX in the treatment of immunocompromised patients across all age groups was consistent with that observed in the treatment of influenza in non-immunocompromised patients (otherwise healthy patients or "at risk" patients, e.g., those with respiratory and/or cardiac co-morbidities).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety App (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

In overdose, symptoms may be the exacerbation or exaggeration of side effects.

Treatment is supportive and symptomatic.

Paediatric population

Overdose has been reported more frequently for children than adults and adolescents. Caution should be exercised when administering OSELTREX to children.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 20.2.8 Antiviral medicines

Pharmacotherapeutic group: Antivirals for systemic use, neuraminidase inhibitors

ATC code: J05AH02

Mechanism of action

Oseltamivir phosphate is a prodrug of the active metabolite (oseltamivir carboxylate). The active metabolite is a selective inhibitor of influenza virus neuraminidase enzymes, which are glycoproteins found on the virion surface. Viral neuraminidase enzyme activity is important both for viral entry into uninfected cells and for the release of recently formed virus particles from infected cells, and for the further spread of infectious virus in the body.

Oseltamivir carboxylate inhibits influenza A and B neuraminidases. Oseltamivir phosphate inhibits influenza virus infection and replication *in vitro*. Oseltamivir given orally inhibits influenza A and B virus replication and pathogenicity *in vivo*. Oseltamivir carboxylate reduces shedding of both influenza A and B virus by inhibiting the release of infectious virus from infected cells.

5.2 Pharmacokinetic properties

Absorption

Oseltamivir is readily absorbed from the gastrointestinal tract after oral administration of oseltamivir phosphate (prodrug) and is extensively converted predominantly by hepatic esterases to the active metabolite (oseltamivir carboxylate). Plasma concentrations of the active metabolite are measurable within 30 minutes, reach near maximal levels in 2 – 3 hours post dose; and substantially exceed (> 20 fold) those of the prodrug. At least 75 % of an oral dose reaches the systemic circulation as the active metabolite.

Plasma concentrations of both the prodrug and active metabolite are proportional to dose and are unaffected by co-administration with food.

Distribution

The mean volume of distribution at steady state of the oseltamivir carboxylate is approximately 23 litres in humans, a volume equivalent to extracellular body fluid. Since neuraminidase activity is extracellular, oseltamivir carboxylate distributes to all the sites of influenza infection.

The binding of the oseltamivir carboxylate to human plasma protein is negligible (approximately 3 %). The binding of the prodrug to human plasma protein is 42 %. These levels are insufficient to cause significant medicine interactions.

Biotransformation

Oseltamivir is extensively converted to oseltamivir carboxylate by esterases located predominantly in the liver. Neither oseltamivir nor the active metabolite is a substrate for, or an inhibitor of, the major cytochrome P450 isoforms (see section 4.5).

Elimination

Absorbed oseltamivir is primarily (> 90 %) eliminated by conversion to oseltamivir carboxylate. The active metabolite is not further metabolised and is eliminated in the urine. Peak plasma concentrations of oseltamivir carboxylate decline with a half-life of 6 – 10 hours in most subjects. The active metabolite is eliminated entirely by renal excretion. Renal clearance (18,8 L/h) exceeds glomerular filtration rate (7,5 L/h) indicating that tubular secretion occurs in addition to glomerular filtration. Less than 20 % of an oral radiolabelled dose is eliminated in faeces.

Pharmacokinetics in special patient groups

Renal impairment

Administration of 100 mg oseltamivir phosphate twice daily for 5 days to patients with various degrees of renal impairment showed that exposure to oseltamivir carboxylate is inversely proportional to declining renal function (see section 4.2).

Hepatic impairment

In vitro studies have shown that exposure to oseltamivir is not expected to be increased significantly nor is exposure to the active metabolite expected to be significantly decreased in patients with hepatic impairment (see section 4.2).

The safety and pharmacokinetics in patients with severe hepatic impairment have not been studied.

Elderly

Exposure to the active metabolite at steady state was 25 – 35 % higher in older people (age 65 – 78 years) compared to adults less than 65 years of age given comparable doses of oseltamivir. Half-lives observed in older people were similar to those seen in young adults. On the basis of medicine exposure and tolerability, dosage adjustments are not required for older people unless there is evidence of moderate or severe renal impairment (creatinine clearance below 60 ml/min) (see section 4.2).

Paediatric population

Children 1 year of age or older: The pharmacokinetics of oseltamivir have been evaluated in single-dose pharmacokinetic studies in children and adolescents 1 – 16 years of age. Multiple-dose pharmacokinetics were studied in a small number of children enrolled in a clinical efficacy study. Younger children cleared both the prodrug and its active metabolite faster than adults, resulting in a lower exposure for a given mg/kg dose. The rate of clearance or the active metabolite increased with decreasing age over the age range 3 – 16 years. Doses of 2 mg/kg give oseltamivir carboxylate exposures comparable to those achieved in adults receiving a single 75 mg dose (approximately 1 mg/kg). The pharmacokinetics of oseltamivir in children and adolescents 12 years of age or older are similar to those in adults.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Crospovidone type A (E 1202)

Microcrystalline cellulose type 101 and 102 (E 460)

Magnesium stearate (E 572)

Povidone K30 (E 1201)

Silica colloidal anhydrous (E 551)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of container

Carton box containing 10, 20 or 30 tablets, packed in blisters of OPA/Aluminium/PVC and Aluminium foil.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

Activo Health (Pty) Ltd

Block B, Arena Office Park

272 West Avenue

Centurion

0157

8. REGISTRATION NUMBER(S)

57/20.2.8/0502

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20 January 2026